Remarks

A. Status of Claims

Claims 14, 15, 18-24, and 30-46 were pending. Claims 30-33 are amended. Claims 39-46 are withdrawn without traverse. Claims 14, 15, 18-24, and 30-38 are now pending.

Amendments to claims 30-33 simply correct inadvertent typographical errors in claim dependency that were discovered by the Office and therefore comply with all rules regarding amendments made after a final rejection. *See, e.g.*, 37 C.F.R. §1.116. No other amendments are being presented.

No new matter has been added.

B. Restriction Requirement

The Office has restricted claims 39-46 as drawn to methods. *See* Office Action, pp. 2-3. Applicants withdraw those claims without traverse. Applicants note that the cover page of the Office Action incorrectly lists the claims that are withdrawn.

C. Section 112, 2nd Paragraph

Applicants thank the Office for its discovery of typographical errors in claims 30-33. Those claims have been amended to correct the inadvertent errors in claim dependency. Applicants respectfully submit that the amendments overcome the current Section 112 rejection.

D. Section 103

Claims 14, 15, 18-19, 22-24, and 34-38 stand rejected as being allegedly obvious in view of WO 94/2117 (Nicolau) in combination with U.S. Patent No. 4,370,983 (Lichtenstein) or U.S. Patent No. 6,090,617 (Meserol). Applicants respectfully traverse.

1. Meserol Is Not Prior Art

Meserol is not prior art. The present application claims priority to, and finds support in, U.S. Patent No. 5,720,921 (*see, e.g.*, cols. 25–26 and figures 14 and subsequent of the '921 patent). The claims therefore have a filing date at least as early as March 10, 1995. Meserol has an effective filing date of December 5, 1996. Because Meserol is not prior art, the arguments below focus on the combination of Nicolau with Lichtenstein.

2. Nicolau Does Not Teach or Suggest the Elements of the Rejected Claims

Rejected independent claims 14, 22, and 34 recite a computer-controllable pump configured in a particular way or a computer itself configured in a particular way. Specifically, amended claim 14 requires, "a computer-controllable pump ... configured to establish a flow rate of the fluid flow path in accordance with a sample processing rate." Claim 22 requires, "a computer responsive to the rate at which the pump moves the biological particles along the fluid flow path and to the interval between pulses of electrical energy." Claim 34 requires, "a computer configured to (a) control charging of the electrodes and (b) establish a flow rate of the fluid flow path in accordance with a sample processing rate." None of these features are taught or suggested by Nicolau.

The Office points to the following passage in support of its rejection concerning these computer-related elements:

> The flow electroporation chamber may be constructed either as a part of the entire flow encapsulation apparatus, or as an individual apparatus. The flow electroporation apparatus may then be connected to a commercially available plasmaphoresis machine for encapsulation of particular cell populations. For example, the flow electroporation chamber may be connected to commercially available plasmaphoresis equipment by electronic or translational hardware or software. **Optionally, a pinch-valve array and controller driven by a PC program can also be used to control the flow electroporation apparatus**. Similarly, current power supplies are capable of establishing the power levels needed to run the flow electroporation chamber or flow encapsulation apparatus.

Nicolau, p. 40 (emphasis added).

The Office acknowledges that Nicolau does not disclose any software or algorithm for making the computer presently being claimed but asserts obviousness in view of this passage and Lichtenstein. *See* Office Action, pp. 5-6.

The above passage indicates that one could optionally use a **pinch-valve array controller** that is driven by a PC program to control a flow electroporation apparatus. *See* Nicolau, p. 40. As clear from Nicolau, such a "controller" could control an "array" (a grouping or arrangement) of a specific type of valve—a "pinch valve" (a valve that seals by way of a pinching action). *See* Nicolau, p. 40. Material behind Tab 1 describes pinch valves; Applicants are not relying upon this material but include it in case the Office would find it useful for background information.

Notwithstanding its disclosure of a pinch-valve array controller, Nicolau nowhere discloses or suggests a computer-controllable **pump** to establish a flow rate in accordance with a sample processing rate (claim 14), a **computer** responsive to a particular pump rate and to an interval of electrical pulses (claim 22), or a **computer** configured to (a) control charging of electrodes and (b) establish a flow rate in accordance with a sample processing rate (claim 34). A computerized pinch-valve array controller is a completely different component than the computer-controlled pump or particularly-configured computers recited in the claims, and disclosure of one does not, and cannot, teach or suggest the others.

Moreover, because pinch-valves operate in a binary manner to either allow flow or to pinch it off completely, pinch-valves are not even designed for tasks such as establishing or being responsive to a particular flow rate, as required by the claims.[1] *See* Declaration of Dr. Sergey M. Dzekunov, Tab 2.

3. *Lichtenstein Does Not Disclose or Suggest the Elements of the Rejected Claims*

Lichtenstein does not "fill the gap" of the missing teaching or suggestion of the particular computer-controlled pumps or computers of the rejected claims. Lichtenstein is cited for the broad proposition that a computer can be a "main integral part" of a medical apparatus. *See* Office Action, p. 6.

With respect to independent claims 14 and 34, Lichtenstein nowhere teaches or suggests the computer-controllable pump or computer configured to establish a flow rate in accordance with the sample processing rate for electroporation. In fact, nowhere does Lichtenstein mention anything about electroporation, much less how (or why) one could or would configure a computer or pump in accordance with its associated processing rate. With respect to claim 34, Lichtenstein is likewise silent as to a computer configured to control charging of electroporation electrodes. With respect to claim 22, Lichtenstein does not teach or suggest a computer responsive to (a) the rate at which a pump moves biological particles along a fluid flow path and (b) to an interval between pulses of electrical energy for electroporation. In fact, it nowhere recognizes such a pulse interval, much less that the interval and a flow rate should correspond in any way.

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[1] This argument, or any other argument, does not disavow claim scope coverage for products that include one or more pinch-valves or a pinch-valve array controller. The claims can cover such products as long as they include the recited elements. What Applicants are stressing is that Nicolau's disclosure of pinch-valves does not constitute a disclosure of the particularly configured pumps and/or computers of the claims—Applicants are not asserting that the claims cannot encompass devices utilizing pinch-valves.

With respect to all the claims, even if computers of Lichtenstein are combined with pinch-valves or computerized pinch-valve controllers of Nicolau, there is no teaching or suggestion about how the pinch-valves could be modified or used to establish, or be responsive to, particular flow rates, given the binary nature of pinch-valves. *See* Declaration, Tab 2.

If the Office disagrees with these characterizations, Applicants request a specific citation to any passage of Lichtenstein (or Nicolau) that teaches, suggests, or motivates a computer or computer-controlled pump configured as claimed with respect to the recited sample processing rate and intervals between electroporation pulses.

Even upon combination with Nicolau, these "gaps" in the teachings of the cited reference remain, which prevent the establishment of any *prima facie* case of obviousness, as discussed in more detail below. *See* M.P.E.P. §2142. Applicants correspondingly request removal of the current Section 103 rejection for each rejected claim.

4. There Is No Motivation To Combine

There is no suggestion or motivation to combine Nicolau with Lichtenstein. Lichtenstein nowhere mentions or even suggests electroporation, which is an aspect of each claim. Lichtenstein is instead directed to a generalized system that accepts modular vessel structures and uses a microcomputer to accept a program for a specific patient and that must match the particular modular vessel structure. *See* Lichtenstein, Abstract. Lichtenstein contains no suggestion (much less a disclosure) of elements common in electroporation such as an electroporation chamber and means for generating fields sufficient for electroporation (*e.g.*, particularly-configured electrodes and associated electronic pulsing equipment). Moreover, nowhere does Lichtenstein suggest or motivate combining any computer technology into applications other than the non-electroporation, general fluid applications it mentions, nor does it

provide any instructions about how such a combination could be achieved. Lichtenstein also does not teach or suggest how one could modify or replace pinch-valve arrays so that a particular flow rate could be established. Thus, nothing in Lichtenstein would suggest a combination with Nicolau.

Likewise, nothing in Nicolau suggests or motivates combination with Lichtenstein. Nicolau is directed to electroporation and does not mention the need or desirability for combining its subject matter with subject matter relating to specialized programs such as Lichtenstein's that are designed for a specific patient and match particular modular vessel structures. Further, there is nothing about Nicolau's disclosure of an optional computer-controlled, pinch-valve array controller that would suggest combination with any other computer-related subject, much less computer-related subject matter for applications other than electroporation. Still further, disclosure of the binary pinch-valves of Nicolau do not motivate combination with equipment concerning the establishment of flow rates.

At best, the Office's only support for combining Lichtenstein with Nicolau is that it could be within the capabilities of one of ordinary skill in the art to physically make such a combination. *See* Office Action, p. 6 (arguing that it would be obvious to achieve computer control of "any parameter established in chamber and/or components operated within the apparatus," no matter the specifics, in view of Lichtenstein). However, the courts have held that type of support in an obviousness rejection is insufficient, as a matter of law: "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." M.P.E.P. § 2143.01 (citing *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990)). Further, the contention that Lichtenstein combined with Nicolau would render obvious the computer control of "any parameter" finds no support in

evidence. Lichtenstein does not disclose or suggest the particular type of computer-control contemplated by the claims; the conclusion that Lichtenstein's generalized "computer-controlled medical care system" nevertheless renders the claims obvious amounts to an impermissible, hindsight analysis. *See Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 873 (Fed. Cir. 1985) (noting that it is improper for an Examiner to employ impermissible hindsight in reconstructing the elements necessary to achieve the invention piecemeal from the prior art).

In sum, there is no motivation to combine the cited art, and the Office's purported support is insufficient.

5. There Is No Evidence Concerning a Reasonable Expectation of Success

The Office has not presented any evidence concerning a reasonable expectation of success associated with the combination of Nicolau and Lichtenstein. There is no evidence that an electroporation device requiring a particular set of electrical and mechanical operating conditions to operate (Nicolau) would work with equipment (a) designed for a different application, (b) that does that does not necessarily need to meet any of the operating conditions necessary for electroporation, and (c) that is directed, instead, to a computer that accepts programs for specific patients and that must match specific modular vessel structures.

6. There Is No Prima Facie Case of Obviousness

In order to establish a *prima facie* case of obviousness, the Office must establish each one of the following:

(1) "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings";

(2) "there must be a reasonable expectation of success"; and

(3) "the prior art reference (or references when combined) must teach or suggest all the claim limitations."

M.P.E.P. §2142.

None of the three factors has been established. First, the art, even when combined, does not teach or suggest all the claim limitations and hence factor 3 is not satisfied. *See* Parts D.2 and D.3 above. Second, there is no motivation to combine, and factor 1 is therefore not satisfied. *See* Part D.4 above. Third, there has been no showing of a reasonable expectation of success, so factor 2 is not satisfied. *See* Part D.5 above.

For at least these three independent reasons, there is, and can be, no *prima facie* case of obviousness. Applicants therefore respectfully request the withdrawal of the current Section 103 rejection. Rejected independent claims 14, 22, and 34 (and all of their dependent claims) are in condition for allowance.

E. Double Patenting

Claims 14, 15, 18-24, and 34-38 stand rejected under the judicially created doctrine of obviousness-type double patenting in view of U.S. Patent No. 5,720,921. Applicants are submitting a terminal disclaimer that overcomes this rejection. *See* Tab 3. As the Office and public should be aware, submission of a terminal disclaimer creates no presumption or estoppel regarding the merits of the double-patenting rejection.

F. Conclusion

Applicants believe that they have responded to all outstanding matters for this application and respectfully request that the rejections of all claims be withdrawn. All the claims are patentably distinct from the cited art and comply with Section 112. Applicants look forward to receipt of a Notice of Allowance.

Should the Office have any questions or desire to sustain **any** rejections, the courtesy of a telephone conference with the Examiner and the Supervisor is respectfully requested in advance so that all pending matters may be more efficiently resolved without the need for filing a notice of appeal.

Respectfully submitted,

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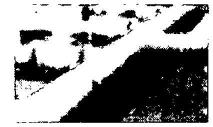

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GLOSSARY

Actuator

Device used to open/close or control the valve. Key types include electrical, hydraulic and pneumatic. Movement may be quarter-turn or multi-turn. Actuators may be used when (i) valves are remotely located (eg, on pipelines) (ii) valves are located in hazardous areas (iii) manual operation would be time-consuming (eg, with larger valves)

Air valve

Valve that is used to control the flow of air. Flows are normally small, so solenoid valves are suited.

Back pressure

The pressure exerted on the downstream side of a valve seat.

Ball valve

A quarter-turn valve with a spherical closing element held between two seats. Characteristics include quick opening and good shut-off. Ball valves are widely used as on/off valves in the chemical process and other industries. Special designs (with V notches or fingers) are available for throttling applications. Larger valves with heavier balls (eg, on pipelines) may use trunnions to help support the ball and prevent damage to soft internals. Designs are typically, one, two or three piece.

Bellows

Sealing device which prevents line media leaking between the stem and the body.

Butterfly valve

A quarter-turn valve which has a circular disk as its closing element. The

standard design has the valve stem running through the disk, giving a symmetrical appearance. Later designs off-set the stem, so that the disk 'cams' into the valve seat. Advantages include less wear and tear on the disk and seats, and tighter shut-off capabilities. Many design types are available including inexpensive Teflon or resilient seats for use in water (treatment) plants, etc. More expensive metal seats can be used where high temperatures or aggressive chemicals are encountered. So-called "High Performance" butterfly valves offer zero leakage designs and have been applied in both the chemicals and hydrocarbon processing sectors.

Bypass valve

A small bore valve fitted in parallel to a larger main valve. Bypass valves are used to reduce the differential pressure across the main valve before this latter valve is opened (as otherwise this larger, more expensive valve, may suffer damage to internal components).

Check valve

A valve that is designed to allow the fluid to flow in a given direction but closes to prevent backflow. Types include swing check, tilting disc check and wafer check. Check valves (also called non-return valves) are usually self-acting.

Control valve

A valve which regulates the flow or pressure of a fluid. Control valves normally respond to signals generated by independent devices such as flow meters, temperature gauges, etc. Control valves are normally fitted with actuators and positioners. Pneumatically-actuated globe valves are widely used for control purposes in many industries, although quarter-turn types such as (modified) ball and butterfly valves may also be used.

Cryogenic valves

These are valves suited for use at temperatures below - 40 degrees Celsius.

Diaphragm valve

A bi-directional valve which is operated by applying an external force to a flexible element, or diaphragm (typically an elastomer). Diaphragm valves may be used for slurries (where other valve designs might clog) or in hygienic applications.

Diverter valve

A valve which can change the direction of the flow of a medium to two or more different directions.

Double block and bleed

A valve configuration in which positive shut-off is achieved at both the inlet and outlet sides. A small port is fitted to discharge fluid in the intermediate space. Fitting a gas detector to the port provides assurance of the integrity of the upstream seal. This configuration is often required to isolate high pressure sections of a system to facilitate safe maintenance, etc.

Electric actuators

Actuator which uses an electric motor to operate the valve stem.

Extended bonnet

Used when the media is at high or low temperatures, to avoid damage to the sealing elements.

Float valve

A valve which automatically opens or closes as the level of a liquid changes. The valve is operated mechanically by a float which rests on the top of the liquid.

Full bore

Term used e.g. of a ball valve, to indicate that the internal diameter of the valve opening is the same as that of the piping to which it is fitted.

Gate valve

A multi-turn valve which has a gate-like disk and two seats to close the valve. The gate moves linearly, perpendicular to the direction of flow. This type of valve is normally used in the fully opened or fully closed position; it is not suited to throttling applications. Gate valves provide robust sealing, and are used extensively in the petrochemicals industries. This class of valves also includes knife gate valves, conduit gate valves and wedge gate valves. Knife gate valves have much thinner gates with a knife-like edge, making them suited to use with floating solids, eg, as in the pulp & paper industries. Conduit gate valves have a rectangular disk as the closing element. One half of the disk is solid, to close the valve, the other has a circular port, which can be used to open the valve. Wedge gate valves have a wedge-shaped gate which 'wedges' between floating seats to close the valve tightly.

Gearboxes

Used to ensure easier operation of larger valves, particularly ball valves.

Globe valve

A multi-turn valve with a closing element that moves perpendicularly to the valve body seat and generally seals in a plane parallel to the direction of flow. This type of valves is suited both to throttling and general flow control.

Hydraulic actuator

A device fitted to the valve stem than uses hydraulic energy to open and close the valve. Depending on the configuration, the hydraulic fluid may both open and close the valve, or just open the valve. In that latter case, a spring will typically be fitted inside the actuator to return it (and the valve) to the closed position.

Jacketed valve

This valve is design incorporates a so-called jacket around the valve body. Steam is introduced into the jacket to keep the fluids being controlled at the required temperature.

Lift check

This non-return valve design incorporates a piston to damp the disk during operation.

Line blind

A pipeline shut-off device, whereby a flat disk is forced between two flanges. Line blinds are less expensive than valves, but require much more time to operate.

Linear valve

See multi-turn

Multi-ported

Multi-ported valves include additional inlet/outlet ports, to allow fluids to be directed. The ball and plug valve types are ideally suited to multi-port designs.

Multi-turn

Category of valves (such as gate, globe, needle) which require multiple turns of the stem to move the valve from the fully open to the fully closed position. Also known as linear valves. See also quarter-turn.

Needle valve

This multi-turn valve derives its name from the needle-shaped closing element. The design resembles that of the globe valve. Typically available in smaller sizes, they are often used on secondary systems for

on/off applications, sampling, etc.

Penstock valve

A type of simple gate valve, used to contain fluids in open channels. Often found in waste water treatment plants.

Pilot valve

Small valve requiring little power which is used to operate a larger valve. See also solenoid valves.

Pinch valve

A valve in which a flexible hose is pinched between one or two moving external elements to stop the flow. This valve is often used in slurry and mining applications, as its operation is not affected by solid matter in the medium. It is also used with certain gases, as the absence of possible leak paths to the atmosphere ensures good emission control.

Plug valve

This multi-turn valve derives its name from the rotating plug which forms the closing element. The plug may be cylindrical or truncated. In the open position, the fluid flows through a hole in the plug. Lubricated plug valves rely on a sealing compound injected between the plug and the valve body, whilst sleeved plug valves are fitted with a 'soft' insert between the plug and the body.

Pneumatic actuator

A device fitted to the valve stem than uses pneumatic energy to open/close or regulate the valve. Depending on the configuration, the compressed air may both open and close the valve, or just open the valve. In that latter case, a spring will typically be fitted inside the actuator to return the valve to the closed position.

Positioner

Device that ensures the closing or throttling element of a valve moves to or maintains the correct position.

Pressure reducing valve

A self-operating valve used to reduce any excess pressure in a system, eg steam. Also known as a PRV. The valve opens if the internal pressure exceeds that holding the closing element onto the seat.

Quarter-turn

Category of valves (such as ball, plug, butterfly) which require just a 90

degree turn of the stem to move from the fully open to the fully closed position. See also multi-turn. Note: some larger valves may, for simpler manual operation, be fitted with gearboxes, giving them the appearance of a multi-turn valve.

Reduced bore

Indicates that the internal diameter of the valve is lower than the piping to which the valve is fitted.

Regulating valve

This valve type is used to regulate flows to provide a constant pressure output.

Sampling valve

A valve which is fitted to a reactor or pipeline to allow small sample of a fluid to be withdrawn for further testing. In simple cases a standard gate or needle valve, for example, may be used. The disadvantage is, that inappropriate use may result in spillage. As an alternative, valves are available which 'trap' a small quantity of fluid in a chamber, and only this small amount of fluid is released when the valve is operated.

Solenoid valve

Solenoid valves, typically of the needle globe type, are operated by an electrical solenoid. They are often deployed as pilot valves, i.e., fitted to actuators which in turn control larger valves.

Spring return

See Pneumatic actuator.

Subsea valve

A valve which is designed for use in sea water. For example, installed in a pipeline on the sea bed.

Swing check

This non-return valve has a hinged disk as the closing element.

Tank valve

A valve arranged for fitting at the bottom of a tank or process vessel.

Wafer design

The construction of wafer design valves allows them to be 'sandwiched' between flanged sections of pipeline. The benefit is lower bolting

requirements. Typically used with certain butterfly and check valves.

Wellhead valve

Wellhead valves are used to isolate the flow of oil or gas at the takeoff from an oil or gas well. The design is usually a plug or gate valve.

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37 C.F.R. 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, P. O. Box 1450, Alexandria, VA, 22313-1450, on the date below:

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Holaday *et al.*	Group Art Unit: 1632
Serial No.: 09/707,928	Examiner: Dave Trong Nguyen
Filed: November 8, 2000	Atty. Dkt. No.: MAXC:008USC1
For: FLOW ELECTROPORATION CHAMBER AND METHOD	

DECLARATION OF DR. SERGEY DZEKUNOV UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Sergey M. Dzekunov, declare that:

1. I am the Director of Research of MaxCyte, Inc.; 9640 Medical Center Drive; Rockville, MD 20850.

2. I am experienced in the field of electroporation and have designed and operated electroporation devices, including devices using pinch-valves.

3. Pinch-valves are not designed to establish a flow rate in accordance with an electroporation processing rate or pulsing interval. Instead, they function in a binary manner to allow a flow or to pinch it off completely.

4. All statements made of my knowledge are true, and all statements made on information and belief are believed to be true, and these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the referenced patent application or any patent issued on it.

Nov 25, 2003

Date

Sergey M. Dzekunov, Ph.D.